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Synthesis of l-(Alkoxymethyl)-5-benzyl-6-methyluracil as Potential Nonnucleoside HIV-1 RT Inhibitors

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Abstract: 1,3-Dibenzyl-6-methyl-5-zincbromomethyluracil **6** was prepared starting from 6-methyluracil **1**. The cross-coupling reaction of benzylic zinc reagent **6** with PhI using bis(dibenzylideneacetone) palladium(0) and (o-furyl)$_3$P as catalyst gave 1,3,5-tribenzyl-6-methyluracil **7**. The N-1,N-3-dibenzyl group could be removed in dealkylation to give the 5-benzyl-6-methyluracil **8**. It was N-1-alkylated with chloromethyl ethyl ether or chloromethyl benzyl ether to obtained the targets **9a** and **b**. All synthesized compounds were tested for their inhibition of HIV-1 reverse transcriptase, and moderate activity were found for target compounds **9a** and **b** and **5**.

Keywords: HIV-1 reverse transcriptase, nonnucleoside reverse transcriptase inhibitors, N-1-alkylated-5-benzyl-6-methyluracil

Since the discovery of the human immunodeficiency virus (HIV) as the causative agent of acquired immunodeficiency syndrome (AIDS),[1,2] among the potential targets for antiviral chemotherapy, HIV-1 reverse transcriptase (HIV-1 RT) and HIV-1 protease have been successful to date. Nucleoside analogues, such as 3′-azido-3′-deoxythymidine (AZT),[3] are useful drugs against HIV. However, these compounds exhibit significant toxicity and viral resistance.[4] Therefore, the development of very specific and highly active nonnucleoside inhibitors of HIV-1 RT was envisioned to be the potential solution for HIV-1 infection. Nonetheless, these agents also failed

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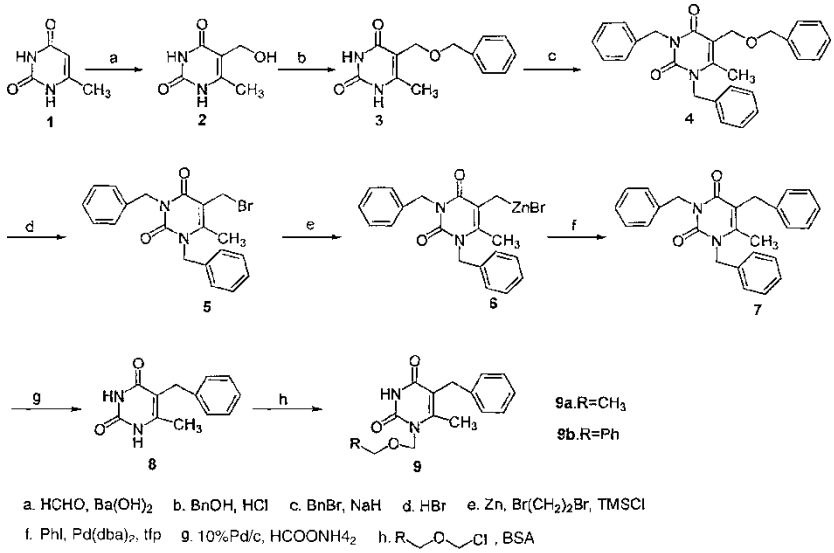
to deal with viral resistance; it is necessary to continue the search for new and more effective anti-HIV agents.

Nonnucleoside reverse transcriptase inhibitors (NNRTI) of HIV are a very broad class of structurally diverse molecules. Within the group of nonnucleoside inhibitors of HIV-1 RT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine[5] (HEPT) is one of the potential candidates for further development in the search for an effective agent. Now, the new HEPT derivatives such as MKC-442, GCA-186, and TNK-651 show greater inhibitory effects than the parent compounds.[6] Although extensive structure–activity relationships on the anti-HIV activity have been performed, only a few investigations have dealt with the variation of the 5-substituent in the uracil ring. Little or no information is available about 5-aromatic and 6-small substituents. We therefore decided to synthesize N-I-alkylated, 5-benzyl, and 6-methyl group uracils as examples of 5-bulky and 6-small substituents to find out whether the new NNRTI type drugs display a high level of activity against the clinically revant HIV mutant strains.

1-(Alkoxymethyl)-5-benzyl-6-methyluracil was prepared by 6-methyluracil as a starting material (Scheme 1). For the preparation of the target compounds **9**, commercially available 6-methyluracil **1** was first hydroxy methylated with an excess of HCHO in $Ba(OH)_2$ to give 5-hydroxymethyl-6-methyluracil **2** in 80% yield, using the same conditions as used in the synthesis of the corresponding uracil derivative.[7] 1 Compound **2** reacted with benzyl alcohol in aqueous HCI according to literature procedures to give the 5-benzyloxymethyl-6-methyluracil **3** in 80% yield and then



Scheme 1.

underwent N-benzylation with 2 molar equivalents of sodium hydride and 2 molar equivalents of benzylbromide in dry DMF to furnish 1,3-dibenzyl-5-benzyloxymethyl-6-methyluracil **4**.

1,3-Dibenzyl-5-bromomethyl-6-methyluracil **5** was prepared by treating **4** with 33% HBr solution in acetic acid in 57% yield. The zinc compound **6** was obtained via the slow addition of **5** to zinc powder previously activated by treatment with 1,2-dibromoethane and trimethylsilychloride (TMSCI).[8] The compound **6** was easily converted to 1,3,5-tribenzyl-6-methyluracil **7** by treatment **6** with iodobenzene in THF in the presence of a catalytic amount of bis(dibenzylideneaceton)palladium(0) [$Pd(dba)_2$] and $(o\text{-furyl})_3P$[9] (tfp) after 12 h at room temperature in 81% yield, together with minor 1,3-dibenzyl-5,6-dimethyluracil.

The deprotection of the benzyl group for **7** was unsuccessful with usual reagents such as $TiCl_4$,[10] CAN,[11] DDQ,[12] and TFA,[13] which gave no or multiple products. However, deprotection with $HCOONH_4$–10% Pd/C[14] afforded the pyrimidine **8** in 60% yield. It is noteworthy that the deprotection at N-3 is preferable to that of at N-1; the preference at the 3-position of deprotection is because of a more stable N-1-benzyl than that at the 3-position. The alkylation gave the target compounds **9a** and **9b** in 67% and 71% yields, respectively, using standard conditions.[15]

The compounds **3–5** and **7–9** were tested for antiviral activity against HIV-1 RT using HIV antigen detection ELISA; only compounds **5** ($IC_{50} = 26\ \mu M$), **9a** ($IC_{50} = 30\ \mu M$), and **9b** ($IC_{50} = 20\ \mu M$) showed higher activity against HIV-1 RT than reference compound HEPT ($IC_{50} = 53\ \mu M$) but lower than nevirapine ($IC_{50} = 2\ \mu M$).

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC). NMR spectra were recorded on a JNM-AL-300 NMR spectrometer at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR with TMS as the internal standard. Mass spectra were obtained, and the ionization methods used for the mass spectrometry were desorption electron impact-ionization (EI). Melting points were determined on a X_4-type melting-point apparatus. IR was recorded on an Avatar 360 FT-IR spectrometer. Elemental analyses were performed on a Vario EL III and were within $\pm 0.4\%$ of the theoretical values. THF was distilled from sodium/benzophenone prior to use. DMF and CH_3CN were dried and freshly distilled over CaH_2.

5-Hydroxymethyl-6-methyluracil (2)

5-Methyluracil (2.0 g, 15.9 mmol) was added to a filtered solution of $Ba(OH)_2 \cdot 8H_2O$ (1.5 g, 36.0 mmol) in water (20 mL). A solution of 37%

aqueous formaldehyde (4.1 mL, 54 mmol) was added, and the reaction mixture was refluxed for a few minutes to dissolve the 6-methyluracil. The reaction mixture was allowed to stir for 24 h at room temperature, and CO_2 (gas) was bubbled into the reaction mixture to precipitate $BaCO_3$. After filtration, the water was evaporated, and the viscous residue was dissolved at reflux in EtOH (20 mL). The desired product crystallized at room temperature as a pure white solid **2** (1.97 g, 80%); mp $>300^{\circ}$C (lit.[16] mp $>300^{\circ}$C). IR (KBr): 3414, 2933, 1704, 1665, 1447 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 10.94$ (s, IN, N3-H), 10.74 (s, 1H, NI-H), 4.52 (s, 1H, OH), 4.14 (s, 2H, CH_2), 2.12 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 64.2, 151.4, 150.9, 109.2, 62.8, 15.8. MS (EI, 70 eV): m/z (%) = 127 (39), 138 (100), 155 (38), 156 (70) [M^+].

5-Benzyloxymethyl-6-methyluracil (3)

A suspension of 5-hydroxymethyl-6-methyluracil **2** (2.0 g, 12.8 mmol) and aqueous HCl (1 mL) in benzyl alcohol (50 mL) was refluxed for 1 h, resulting in the formation $_{\text{I}}$ of a clear solution. After being cooled to room temperature, the reaction mixture was poured into ether (250 mL). The resulting fine precipitate was filtered and washed several times with ether to give the pure product **3** (2.51 g, 80%); mp $>300^{\circ}$C. IR (KBr): 3433. 1721, 1643, 1447, 1071 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 11.04$ (s, IH, N3-H), 10.90 (s, lH, N1-H), 7.31 (s, 5H, Ph-H), 4.49 (s, 2H, CH_2), 4.22 (s, 2H, CH_2), 2.10 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 164.1$, 153.0, 150.8, 138.6, 128.2, 127.6, 127.4, 105.9, 71.2, 61.8, 15.9. MS (EI, 70 eV): m/z (%) = 140 (100), 155 (5), 247 (0.25) [$M + H^+$]. Anal. calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.20; H, 5.67; N, 11.15.

1,3-Dibenzyl-5-benzyloxymethyl-6-methyluracil (4)

A suspension of 5-benzyloxymethyl-6-methyluracil **3** (3.0 g, 12.2 mmol) in dry DMF (40 mL) was treated portionwise with sodium hydride (1.16 g, 29.0 mmol, 60% in oil). After the end of gas evolution, the reaction mixture was stirred for 1 h at room temperature and benzyl bromide (3.5 mL, 26.5 mmol) was slowly added. The reaction mixture was poured into water (120 mL), and the solvent was evaporated using a rotatory evaporator and then a vacuum pump (0.1 mmHg). The residue was dissolved in EtOAc (60 mL) and was washed with water (30 mL). The aqueous phase was extracted with EtOAc (2 $\times$ 25 mL), and the combined organic phase was washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the crude residue was purified by chromatography [petroleum ether

(60–90°C)–EtOAc, 4:1], providing the desired product **4** (2.95 g, 57%) as colorless oil.

IR (KBr): 3432, 1700, 1649, 702 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.51–7.11$ (m, 15H, 3Ph-H), 5.19 (s, 2H, N3-CH_2), 5.13 (s, 2H, N1-CH_2), 4.53 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 2.20 (s, 3H, CH_3). MS (EI, 70 eV): m/z (%) = 91 (100), 299 (28), 320 (22), 321 (3), 427 (1) [$M + H^+$].

5-Bromomethyl-1,3-dibenzyl-6-methyluracil (5)

Dry 1,4-dioxane (7.85 mL) and 33% HBr-AcOH (3.7 mL 9.7 mmol) were added to 1,3-dibenzyl-5-benzyloxy-6-methyluracil **4** (2.0 g, 4.69 mmol), resulting in the formation of a clear solution. The reaction mixture was stirred for 12 h at room temperature, and the solvent was removed by vacuum to afford an oily residue that crystallized after the addition of a few drops of ether. It was filtrated and washed with ether (1.5 mL) to give product **5** (1.1 g, 59%), which was analytically pure; mp 89–91°C. IR (KBr): 3429, 1701, 1649, 1455, 699 cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 7.52–7.12$ (m, 10H, Ph-H), 5.20 (s, 2H, N3-CH_2), 5.19 (s, 2H, Nl-CH_2), 4.46 (s, 2H, CH_2), 2.27 (s, 3H, CH_3). Ms (EI, 70 eV): m/z (%) = 91 (100), 319 (17), 399 (0.1) [$M + H^+$].

The Zinc Reagent (6)

A dry 50-mL three-necked flask equipped with a nitrogen inlet, a nitrogen venthole, and a thermometer was charged with zinc dust (0.85 g, 13.1 mmol). The flask was flushed with nitrogen, and 1,2-dibromoethane (0.038 mL) in THF (1 mL) was added. The zinc suspension was heated three times to reflux with a heat gun for ca. 30 s and was allowed to cool to room temperature. TMSCl (0.13 mL) was added, and the reaction mixture was stirred for 5 min and cooled to 0°C with an ice bath. The 5-bromomethyl-1,3-dibenzyl-6-methyluracil **5** (1.45 g, 3.6 mmol) in THF: (6 mL) was slowly added using a syringe pump (1 drop every 5 s), and the reaction mixture was stirred for another 30 min at room temperature after the end of the addition. After completion of the reaction, THF (6 mL) was added, and the zinc was allowed to settle for 1–2 h at rt.

1,3,5-Tribenzyl-6-methyluracil (7)

A dry three-necked flask equipped with a nitrogen inlet, a nitrogen venthole, and thermometer was charged with Pd-$(dba)_2$ (19.2 mg, 0.9 mol%) and tfp (15.33 mg, 1.8 mol%) followed by THF (1.7 mL). The initial red color disappeared after 1 min, leading to a yellow solution. The PhI (0.15 mL) was

added followed by the compound **6** obtained in foregoing reaction. The reaction mixture was stirred for 12 h at room temperature and worked up by pouring in aqueous saturated NH_4Cl solution and extracting with EtOAc. The organic phase was washed with brine and dried ($MgSO_4$), and the residual oil obtained after evaporation of the solvent was purified by flash chromatography [petroleum ether (60–90°C)/EtOAc, 5:1] to give the product **7** as a pale yellow oil (0.43 g, 30%).

^{1}H NMR ($CDCl_3$): $\delta = 7.52–7.12$ (m, 15H, Ph-H), 5.22 (s, 2H, N3-CH_2), 5.16 (s, 2H, N3-CH_2), 3.85 (S, 2H, CH_2), 2.15 (s, 3H, CH_3). MS (EI, 70 eV): m/z (%) = 91 (100), 305 (82), 396 (73), 397 (15) [$M + H^+$].

5-Benzyl-6-methyluracil (8)

HCO_2NH_4 (0.66 g, 10.5 mmol), dry methanol (6 mL), and 10% Pd/C (0.8 g) were added to compound **7** (0.23 g, 0.58 mmol). The mixture was allowed reflex for 5 days. It was then cooled to room temperature and passed through celite, washing extensively with methanol. Removal of MeOH and purification by column chromatography using $CHCl_3$-MeOH (9:1) as solvent for elution afforded **8** (75.3 mg, 60%) as white solid; mp 221–222°C.

IR (KBr): 3428, 2927, 1732, 1636, 530 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 11.02$ (s, 1H, N3-H), 10.74 (s, IH, Nl-H), 7.27–7.15 (m 5H, Ph-H), 2.58 (s, 2H, CH_2), 2.09 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 164.5$, 150.8, 149.1, 140.3, 128.3, 127.9, 125.8, 108.1, 29.2, 16.2. MS (EI, 70 eV): m/z (%) = 91 (32), 215 (50), 216 (100), 217 (18) [$M + H^+$]. Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.30; H, 5.67; N, 12.65.

1-(Ethoxymethyl)-5-benzyl-6-methyluracil (9a)

Compound **8** (15 mg, 0.07 mmol) was suspended in CH_3CN (1 mL), and bis(trimethylisily)acetamide (BSA) (38 μL, 0.16 mmol) was added to the suspension. The mixture became clear after stirring at room temperature for 10 min. Chloromethyl ethyl ether (14 μL, 0.08 mmol) was added to the solution, and stirring continued until no change in the amount of the starting material could be noticed on TLC. After evaporation of the solvent in vacuo, the resulting syrup was purified by column chromatography using $CHCl_3$-MeOH (9:1) to afford **9a** (12.8 mg, 67%) as white crystals; mp 101–102°C.

^{1}H NMR ($CDCl_3$): $\delta = 9.13$ (s, 1H, N3-H), 7.30–7.16 (m, 5H, Ph-H), 5.33 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.65 (q, $J = 6.9$ Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.20 (t, $J = 6.9$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 163.3$, 151.6, 150.6, 139.3, 128.5, 128.0, 126.2, 112.5, 73.1, 64.9, 30.7, 15.7, 15.1. MS (EI, 70 eV): m/z (%) = 59 (100), 215 (52), 274 (70), 275 (15)

$[M + H^+]$. Anal. calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.22. Found: C, 65.49; H, 6.80; N, 9.88.

l-(Benzyloxymethyl)-5-benzyl-6-methyluracil (9b)

Compound **8** (16.2 mg, 0.075 mmol) was suspended in CH_3CN (1 mL), and bis(trimethylisily)acetamide (BSA) (41 μL, 0.17 mmol) was added to the suspension. The mixture became clear after stirring at room temperature for 10 mm. Chloromethyl benzyl ether (17 μL, 0.08 mmol) was added to the solution, and stirring continued until no change in the amount of the starting material could be noticed on TLC. After evaporation of the solvent in vacuo, the resulting syrup was purified by column chromatography using $CHCl_3$-MeOH (9:1) to afford **9b** (19.4 mg, 77%) as white crystals; mp 152–153°C.

IR (KBr): 3434, 1668, 1461 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.24 (s, 1H, N3-H), 7.37–7.16 (m, 10H, Ph-H), 5.43 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 3.80 (s, 2H, CH_2), 2.34 (s 3H CH_3). ^{13}C NMR ($CDCl_3$): δ 163.2, 151.6, 150.4, 139.2, 137.1, 128.7, 128.5, 128.4, 128.0, 127.7, 126.2, 112.6, 73.1, 71.7, 30.6, 15.8 MS (EI, 70 eV): m/z (%) = 77 (16), 91 (100), 215 (38), 336 (17), 337 (4) $[M + H^+]$. Anal. calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.17; H, 6.00; N, 7.95.

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